REMARKS

Any fees that may be due in connection with filing this paper or with this application may be charged to Deposit Account No. 06-1050. If a Petition for Extension of time is needed, this paper is to be considered such Petition. A change of address for the undersigned accompanies this response. Supporting references (Liden *et al.* (1997) *J. Biol. Chem. 272:*21467-21472 and Hard *et al.* (1990) *Science 249*:157-160) also are attached.

Claims 1-3, 5-35, 37-42, 44, 46 and 69-88 are pending. Claims 7, 9, 43 and 45 are cancelled without prejudice or disclaimer. Claim 74-88 are added and claims 1, 6-8, 10, 13, 20, 22, 32, 39, 44 and 73 as set forth below. are amended in order to more particularly point out and distinctly claim the subject matter that applicant regards as the invention.

No new matter is added. For example, claim 1 is amended by incorporation of original claim 10. Basis also can be found in claim 13 and on pages 34-36, which describe addressing of zinc fingers by combining modular portions thereof. The amendment of claims 6-8 and 10 find particular basis in the specification at pages 34-36. For example page 36, *et seq.* recites:

> Studies of natural zinc finger proteins have shown that three zinc finger domains can bind 9 bp of contiguous DNA sequence (Pavletich *et al.* (1991) *Science 252*:809-817; Swirnoff *et al.* (1995) *Mol. Cell. Biol. 15*:2275-2287). While recognition of 9 bp of sequence is insufficient to specify a unique site in a complex genome, proteins containing six zinc finger domains can specify 18-bp recognition (Liu *et al.* (1997) *Proc. Natl. Acad. Sci. USA 94*:5525-5530). An 18-bp address made up of modular units is of sufficient complexity to specify a single site within all known genomes . . ..
>
> Zinc finger-nucleotide binding polypeptide variants can be constructed from known motifs. The variants include at least two and preferably at least about four zinc finger modules that bind to a cellular nucleotide sequence, such as DNA, RNA or both, and specifically bind to and modulate the function of a cellular nucleotide sequence.

Claims 22 and 25 are amended to properly depend from claim 1.

Claim 74-88 are added. These claims correspond to original claims in the parent application U.S. application Serial No. 09/433,042, which is incorporated by reference into this application, and throughout the instant application, such as page 4, which recites;

> In a preferred embodiment, the isolated recombinant fusion protein forms a dimer when bound to a polynucleotide. The dimer can be a homodimer or a heterodimer. In one embodiment, the dimer includes at least one DNA binding domain, at least one, preferably two, ligand binding domains and at least one transcription modulating domain. In heterodimers, the dimer can include two different DNA binding domains, two different ligand binding domains or two different transcription modulating domains. One exemplary heterodimer includes at least three zinc finger modular units, two different ligand binding sites and a transcription modulating domain.

Basis also can be found at page 10, which recites:

> Upon administration, the ligand binds to the ligand binding domain of the fusion protein, whereby the DBD of the fusion protein, either as a monomer or dimer, interacts with a targeted gene and transcription of the targeted gene is repressed or activated. As noted, the targeted gene may be an endogenous gene or an exogenously administered gene.

Information Disclosure Statements

It is noted that a continuation application, U.S. application Serial No. 10/422,934, was filed on April 23, 2003. The Examiner's attention also is to U.S. Patent No. 6,242,568 corresponding published International PCT application No. WO 95/19431 and published US application 20030059767 as well as other applications with an owner or inventor in common with the instant application. Such patents and published applications are of record in Information Disclosure Statements filed in connection with this application.

RESTRICTION REQUIREMENT

Responsive to Applicant's arguments against the restriction requirement and election of species in the previous action, the election of species has been withdrawn based upon Scheller *et al.* cited in the instant Office Action. The species previously elected was the estrogen receptor. Scheller *et al.* is directed

to chimeric androgen and glucocorticoid receptors. It is maintained, however, that SEQ ID. NOS. 1-18, set forth as exemplary fusion proteins in the instant application, are restrictable and SEQ ID. NOS. 2-18 will not be rejoined because they are not elected species but constitute "independent and distinct inventions, which require non-coextensive searches, and a search of one of the sequences would not reveal art on any of the other sequences, thus imposing a burden on the Examiner." The Examiner states that the generic claims, along with the remaining pending claims, have been restricted to a fusion protein encoded by a single nucleotide sequence, namely, SEQ ID. NO. 1.

Applicant respectfully submits that Requirement as set forth is incorrect and as set forth was not clear resulting in an election of group I, which the applicant understood to include generic claims to be treated as an election of a one molecule, which includes the sequence of nucleotides set forth in SEQ ID No. 1. Applicant would not necessarily have elected that sequence and certainly would have vigorously argued the propriety of the requirement. As discussed below, the Examiner is not following the rules for restriction of claims to nucleic acid molecules. Furthermore, claim 1 and other claims as originally filed are linking claims that should have been examined with the elected group. Furthermore, if the linking claims are found allowable, then all claims linked thereby must be rejoined.

Because the Requirement was not correct, as discussed below, applicant respectfully requests formulation of the requirement into a form that better comports with Rules.

1. Restriction to a single molecule

Restrictions to single nucleotide sequences are discussed in §803.04 of the Manual of Patent Examining Procedure (MPEP). According to MPEP §803.04, claims drawn to nucleotide sequences encoding different proteins are deemed properly restrictable, but the Commissioner has decided *sua sponte* to partially waive this requirement for a reasonable number (usually, ten) of patentably distinct sequences. MPEP §803.04 states:

> Accordingly, in most cases, up to ten independent and distinct nucleotide sequences will be examined in a single application without restriction. In addition to the specifically selected sequences, those sequences which are patently indistinct from the selected sequences will also be examined. Furthermore, nucleotide sequences encoding the same protein are not considered to be independent and distinct inventions and will continue to be examined together.

Accordingly, in this instance, the Examiner allegedly has only permitted examination of a single sequence, SEQ ID No. 1, not the reasonable number, as set forth in MPEP §803.04.

Furthermore, even if restriction to a single specific sequence of nucleotides is permissible, claims, such as claim 1 and claim 32 and dependent claims, as originally filed, and as presently, pending generic claims, such as, are linking claims. Linking claims must be examined with an elected group.

2. Linking claims

It is respectfully submitted that claims 1 and 32 and dependent claims as pending and as originally filed are linking claims. These claims "link" the dependent claims, directed fusion proteins (or encoded fusion proteins) that include specified sequences of nucleotides (*e.g.*, SEQ ID. NOS. 1-18). According to MPEP §809, when claims linking more than one group are found, the Restriction Requirement must be conditioned on 1) specifying the linking claims; and 2) examining the linking claims with the elected group. The linking claims **must** be examined with the elected group, and the Restriction Requirement **must** be conditioned on allowability of the linking claims. If the linking claims are deemed allowable, then the Restriction Requirement must be withdrawn and all claims directed to nonelected subject matter that depends from or includes all the limitations of the linking claims must be rejoined.

In this instance, the Examiner failed to specify the linking claims and it is unclear whether they have been examined, although it appears they may have been. It is respectfully submitted that claims 1 and 32 and claims dependent thereon as presently pending (and claim 1 as originally filed) are linking claims,

since they encompass fusion proteins encoded by SEQ ID No. 1 (claim 1 and dependents) or nucleic acid molecules that encode fusion proteins encoded by SEQ ID No. 1 (claim 32 and dependents). Therefore, claims 1 and 32 are linking claims. If claims 1 and/or 32 are deemed allowable the restriction requirement dividing these claims into 18 groups, must be withdrawn.

Therefore because most of the claims, as pending and originally filed (designed groups I-XVIII by the Examiner) are linking claims, the generic claims should be examined and all of groups I-XVIII rejoined upon a determination that claim 1 and/or claim 32 as presently pending is allowable. Furthermore, since the Commissioner has deemed that more than one molecule per case is permitted, at least 10 of SEQ ID Nos. 1-18 could have been searched (although such search is not necessary if a linking claim is deemed allowable).

3. It appears that the Examiner may be treating more generic claims as linking claims

As evidenced by the citation of Beerli in the previous action and Scheller in the instant action and by the Examiner's own arguments with respect to these documents, the structural and functional elements set forth in the generic claims can be searched by virtue of their properties, *e.g.*, ligand-binding domains of intracellular receptors and zinc finger proteins and it appears that the Examiner has searched these elements and that the rejections are directed thereto. Cited art, such as Scheller *et al.* is cited against claim 1, but does not disclose a fusion protein the includes a sequence of amino acids encoded by SEQ ID No. 1. Scheller *et al.* clearly does not anticipate SEQ ID No. 1 (nor any of the pending claims as discussed below). Briefly, fusion proteins encoded by a molecule comprising SEQ ID No. 1, include C7, a specific C2H2 zinc finger peptide sequence (variant of the murine C2H2 zinc finger protein Zif268) linked to a specific sequence of the estrogen receptor ligand binding domain and a heterologous transactivation domain. Scheller *et al.* discloses none of these elements.

Accordingly, it appears that the Examiner may be treating claims 1, 32 and dependent claims as linking claims. Clarification is requested. g the arguments laid out in the instant office action, it would appear that the Examiner has examined the generic claims. The Examiner relies on the generic structural and functional elements of these claims to show anticipation.

OBJECTION TO CLAIM 22

Claim 22 is objected to as being drawn to non-elected subject matter. In light of the issues with respect to the Restriction Requirement, claim 22 is retained pending resolution of these issues.

THE REJECTION OF CLAIMS 1-3, 5-35, 37-46, 69 and 73 UNDER 35 U.S.C. § 102

Claims 1-3, 5-35, 37-46, 69 and 73 are rejected under 35 U.S.C. §102(b) as being anticipated by Scheller *et al.* (*J. Biol. Chem. 273(37)*:24216-22 (1998)) because Scheller *et al.* discloses chimeric fusion proteins combining amino terminal, DNA binding and ligand binding domains of the androgen and glucocorticoid receptors (AR, GR). It is further alleged that the ligand binding domain of the fusion proteins in Scheller *et al.* are modified to change ligand specificity from the native receptor because the ligand binding domains of AR and GR are interchanged. These fusion proteins allegedly meet the limitations in independent claim 1. The Examiner further alleges that Scheller discloses all the additional limitations in dependent claims 2, 3, 5-7, 9-19, 69 and 73. Independent claim 8 is allegedly anticipated because the chimera proteins of Scheller comprise C2H2 domains in the zinc finger region of the nucleotide binding domain. Independent claim 20 is allegedly anticipated because the chimeras of Scheller *et al.* are ligand activated transcriptional regulators. Dependent claim 21 is allegedly anticipated because there is no structural limitation on the repression domains which the claimed fusion proteins must comprise. Claims 23, 24 and 26-31 are rejected because Scheller *et al.* allegedly discloses nucleic acid encoding the chimeric proteins. Claims 32-38 are rejected because the vectors of Scheller *et al.* allegedly were constructed

using viral vectors. Claims 39-46 are rejected because Scheller *et al.* allegedly discloses the transfection of cells with nucleic acids encoding chimeric receptors and hormone response elements upstream of reporter genes. The Examiner concludes that Scheller *et al.* anticipates the claims.

This rejection is respectfully traversed.

Relevant law

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. In re Spada, 15 USPQ2d 1655 (Fed. Cir. 1990), In re Bond, 15 USPQ 1566 (Fed. Cir. 1990), Soundscriber Corp. v. U.S. 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), cert. denied, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention." In re Lang, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). Moreover it is incumbent on Examiner to identify wherein each and every facet of the claimed subject matter is disclosed in the reference. Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co., 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984).

Further, the reference must describe the claimed subject matter sufficiently to have placed a person of ordinary skill in the art in possession of the claimed subject matter. Prior art does not anticipate a thing or process unless it is enabling; an anticipatory publication must describe the claimed invention with sufficient clarity and specificity so that one skilled in the relevant art could practice the subject matter of the patent without assistance from the patent claimed to have been anticipated Columbia Broadcasting System v. Sylvania Elec. Products, Inc., 415 F.2d 719, 735, 162 USPQ 577 (1st Cir.1968) cert. denied, 396 U.S. 1061, 164 USPQ 321 (1970).

"Before any publication can amount to a statutory bar to the grant of a patent, its disclosure must be such that a skilled artisan could take its teachings in combination with his own knowledge of the particular art and be in

possession of the invention." Titanium Metals Corp. v. Mossinghoff, 603 F.Supp. 87,0, 225 USPQ 673 (1984) quoting In re Application of Le Grice 49 CCPA 1124, 301 F.2d 9333

The claims

Independent claim 1 is directed to a fusion protein that contains a nucleotide binding domain operatively linked to a ligand binding domain from an intracellular receptor. The nucleotide binding domain is a polydactyl zinc-finger that contains at least three modular portions thereof. Each modular portion interacts with a contiguous nucleotide sequence of at least about 3 nucleotides; and the ligand binding domain is modified to change its ligand specificity compared to the ligand specificity of the ligand binding domain of the native hormone receptor. The fusion protein functions as a ligand activated transcriptional regulator.

Dependent claims specify particulars of the components of the fusion protein. Claim 2 specifies that the fusion protein contains an operatively linked transcription regulating domain; claim 3 specifies that the ligand binding domain is from a nuclear hormone receptor. Claim 5 recites that the modified ligand-binding domain is not substantially activated by endogenous ligands relative to exogenous or non-natural ligands. Claim 6 specifies that a module of the zinc-finger peptide binds to a sequence of nucleotides of the formula $(GNN)_n$, where is an integer from 3 to 6; and claim 7 specifies that n is 6, which results in unique specificity for a targeted gene. Claim 8 specifies that the nucleotide binding domain contain 6 C2H2 zinc finger modules and binds to 18 nucleotides so that the nucleotide binding domain has unique specificity for a targeted gene. The fusion protein is a gene-specific ligand activated transcriptional regulator. Claim 10 specifies that the nucleotide binding domain contains 4 modules and claim 73 defines the affinity of the domain for a nucleic acid molecule. Claim 11 specifies a list of nuclear hormone receptors; claim 12 specifies that the intracellular receptor is a steroid receptor; claim 13 recites that the ligand binding domain is from a progesterone or estrogen receptor. Claim 14

specifies that the transcription regulating domain includes a transcription activation domain; claims 15-19 specify particulars of the domain. Claim 20 specifies that the transcription regulating domain includes a transcription repression domain; and claim 21 specifies particular repression domains. Claim 22 is directed to a fusion protein of claim 1 that includes the fusion protein encoded by the sequence of nucleotides set forth in any of Sequence ID Nos. 1-18. Claim 69 recites that the nucleic acid binding domain of the fusion protein interacts with a contiguous nucleotide sequence of about 18 nucleotides.

Claim 74 recites that fusion protein of claim 1 that contains a DNA binding domain, two ligand binding domains and a transcription modulating domain; claim 75 recites that the fusion protein of claim 1 that forms a dimer when bound to a polynucleotide; claim 76 recites that if is a monomer when bound to a polynucleotide; claim 82 recites that it is a heterodimer; and claim 83 recites that the heterodimer contains at least three zinc finger modular units, two different ligand binding sites and a transcription modulating domain. Claims 84-86 also recites that the fusion protein is a dimer and recite components of each monomer; claim 87 recites that the fusion protein of claim 87 is a homodimer and claim 88 recites that it is a heterodimer. Claim 77 recites that the fusion protein contains a second ligand binding domain; claim 78 recites that it is the same as the first binding domain; claim 79 recites that the second ligand binding domain is different from the first binding domain; and claims 80 and 81 recite particular receptors from which the second ligand binding domain is derived.

Claims 23-25 are directed to nucleic acid molecules encoding a fusion protein of claim 1. Claim 24 specifies that the protein includes an operatively linked transcription regulating domain; claim 25 recites that the fusion protein includes C7 C2H2 nucleotide binding domain operatively linked to a ligand binding domain from an estrogen receptor that are encoded by a-sequence of nucleotides set forth in SEQ ID No. 1.

Claims 26, 27, 33, 37 and 38 are directed to vectors that encode the fusion proteins of claim 1 and 2, respectively; and claims 28-31 are directed to cells containing the vectors. Claims 32 and 34 are directed to a viral vector that encodes a fusion protein and specifies that the fusion protein contains a ligand binding domain from an intracellular receptor, wherein the nucleotide binding domain is a polydactyl C2H2 zinc-finger peptide or modular portion thereof that interacts with a contiguous nucleotide sequence of at least about 9 nucleotides; and the fusion protein is a ligand activated transcriptional regulator; claim 34 recites that the viral vector is derived from a DNA virus or a retrovirus and claim 35 recites particular viral vectors.

Claim 39 is directed to a combination that contains a fusion protein of claim 1; or a nucleic acid molecule comprising a sequence of nucleotides that encodes the fusion protein; and a regulatable expression cassette that comprises at least one response element recognized by the nucleic acid binding domain of the fusion protein. Claims 41 and 44 specify that the combination is in the form of a single composition; and claim 42 specifies that the elements of the combination are in separate compositions. Claim 46 specifies that the regulatable expression cassette contain 3 to 6 response elements.

Claims 70-72 are directed to non-viral delivery systems that contain the fusion protein of claim 1 or a nucleic acid molecule encoding the fusion protein.

Thus, there are two independent claims: claim 1 and claim 32.

Claim 1 includes the elements:

a) it is directed to a fusion protein

b) the fusion protein contains:

i) nucleotide binding domain operatively linked to a ligand binding domain from an intracellular receptor;

ii) the nucleotide binding domain is a polydactyl zinc-finger that contains at least three modular portions;

iii) each modular portion interacts with a contiguous nucleotide sequence of at least about 3 nucleotides;

iv) the ligand binding domain is modified to change its ligand specificity compared to the ligand specificity of the ligand binding domain of the native hormone receptor from which it is derived; and

v) the fusion protein functions as a ligand activated transcriptional regulator.

Claim 32 is directed to a viral vector that encodes fusion protein, that has the following elements:

a) a nucleotide binding domain operatively linked to a ligand binding domain from an intracellular receptor;

b) the nucleotide binding domain is a polydactyl C2H2 zinc-finger peptide or modular portion thereof;

c) the nucleotide binding domain interacts with a contiguous nucleotide sequence of at least about 9 nucleotides; and

d) the fusion protein is a ligand activated transcriptional regulator.

Differences between the disclosure of Scheller et al. and the claimed subject matter

Scheller is directed to chimeric fusion proteins containing combinations of the amino terminus, DNA binding and ligand binding domains of the androgen and glucocorticoid receptors (AR, GR) in order to identify features of ARs that are responsible for functional differences from GRs. It is well known that the AR and GR receptor DNA binding domains contain **two** zinc fingers, which have a C4H4 C4 zinc-finger motif (see, *e.g.*, Liden *et al.* (1997) *J. Biol. Chem. 272:*21467-21472, at, for example, page 21467, col.1; Hard *et al.* (1990) *Science 249*:157-160).

Scheller *et al.* further discloses fusion proteins that contain a truncated AR or GR ligand binding domain to assess interaction of the DBD on specificity. The truncation results in a change in cooperative receptor interaction and DNA binding by the DNA binding domain.

Analysis

All of the claims require that the fusion protein contain at least 3 zinc fingers. Since the AR and GR receptors contain only 2 each, Scheller cannot anticipate any of the pending claims.

Claim 1 and dependents

Scheller does not disclose a fusion protein that contains **three** zinc fingers, since the AR and the GR DNA binding domains contain 2 zinc fingers (modules). Furthermore Scheller *et al.* does not disclose fusion proteins containing ligand binding domains that have been modified to change their ligand specificity compared to the native hormone receptors. Scheller *et al.* discloses only chimeric proteins containing nucleotide binding domains fused to ligand binding domains that retain their native ligand specificity. Changing the ligand binding domain of AR with GR or *vis versa* does not meet the limitation of claim 1, which requires that the LDBs have altered ligand specificity compared to the native receptor from which the LBD is derived. As claimed, the ligand binding domain is modified to change its specificity with respect to the native intracellular receptor from which the ligand binding domain originates. The truncation in the ligand binding domain of Scheller *et al.* results in a change in cooperative receptor interaction and DNA binding by the DNA binding domain, but does not change ligand specificity.

Therefore, Scheller *et al.* does not anticipate independent claim 1 nor any claims dependent thereon.

Claim 32

With respect to claims 32 and 34, which are directed to viral vectors that encode fusion proteins containing a DBD and LBD, where the DBD contains at least three C2H2 modules, Scheller does not disclose viral vectors nor vectors that encode fusion proteins that contain at least three C2H2 modules in the DBD.

Scheller *et al.* discloses chimeric proteins containing either androgen or glucocorticoid DNA binding domains, which contain a C4 zinc-finger motif.

Scheller *et al.* does not disclose a zinc-finger peptide comprised of modular units from a C2H2 zinc-finger peptide. Therefore, Scheller *et al.* does not anticipate claims 32 and 34.

Since anticipation requires that a reference disclose all elements as claimed, Scheller *et al.* does not anticipate any of the claims.

THE REJECTION OF CLAIMS 1-3, 5-35, 37-46 and 69-73 UNDER 35 U.S.C. § 103

Claims 1-3, 5-35, 37-46 and 69-73 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over the teachings of Scheller *et al.* (1998) in view of Sibson *et al.* (WO/9401548) because Scheller *et al.* allegedly teaches the claimed fusion proteins but does not teach non-viral vectors. It is further alleged that Sibson *et al.* teaches the use of non-viral vectors and cells to express DNA, as well as methods of producing proteins. The Examiner concludes that it would have been *prima facie* obvious to one of ordinary skill in the art to modified the teachings of Sibson *et al.* by substituting a cDNA in the polycloning region of the vector with the polynucleotide (cDNA) of Scheller *et al.* for the purpose of transfecting a host cells as taught by Sibson *et al.* in view of the suggestion in Sibson *et al.* that it would be desirable to do so (pages 8-13). The Examiner asserts that one of ordinary skill in the art would have been motivated to make this substitution in order to express the protein encoded by the introduced DNA in a host cell to perform ligand binding and functional assays. The Examiner further asserts that one of ordinary skill would have had a reasonable expectation of success since Sibson *et al.* allegedly teaches that these techniques are widely used in the art and are highly successful (Sibson *et al.*, page 10, line 38-page 12, line 42).

This rejection is respectfully traversed.

Relevant law

In order to set forth a *prima facie* case of obviousness under 35 U.S.C. § 103: (1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (*ACS Hospital Systems, Inc. v. Montefiore Hospital*, 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984)) and (2) the combination of the cited references must actually teach or suggest the claimed subject matter. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. *Ex parte Gerlach*, 212 USPQ 471 (Bd. APP. 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art" *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed subject matter, absent some teaching or suggestion supporting the combination (*ACS Hosp. Systems, Inc. v. Montefiore Hosp.* 732 F.2d 1572, 1577. 221 USPQ 929, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" *W.L. Gore & Associates, Inc. v. Garlock Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

The prior art must provide a motivation whereby one of ordinary skill in the art would have been led to do that which the applicant has done. *Stratoflex Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1535, 218 USPQ 871, 876 (Fed. Cir. 1983). In addition, the mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification. *In re Fritch*, 23 USPQ 1783 (Fed. Cir. 1992).

Also, it is impermissible to ignore the advantages, properties, utilities and unexpected results that flow from the claimed invention; they are part of the invention as a whole. *In re Sernaker*, 702 F.2d 989, 217 USPQ 1 (Fed. Cir. 1983). Unexpected properties must always be considered when determining obviousness. A compound's structure and properties are inseparable so that unexpected properties are part of the subject matter as a whole. *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963).

Analysis

The Claims

All pending claims are set forth and discussed above.

Differences between the claims and the combination of teachings of the cited references

Scheller *et al.*

As discussed below, Scheller *et al.* does not teach or suggest a fusion protein containing at least three zinc fingers, nor a fusion protein that contains a ligand binding domain that has been modified to change its ligand specificity. Scheller *et al.* teaches combining a ligand binding domain that retains its native ligand specificity (such as the ligand binding domain of AR) with a nucleotide binding domain from a different hormone receptor (such as the nucleotide binding domain of GR). Simply changing the ligand binding domain of AR with GR or *vis versa* does not meet the limitation of claim 1. As claimed, the ligand binding domain is modified to change its specificity with respect to the native intracellular receptor from which the ligand binding domain originates. The truncation in the ligand binding domain of Scheller *et al.* results in a change in cooperative receptor interaction and DNA binding by the DNA binding domain, but Scheller *et al.* does not teach that this truncation changes ligand specificity. Therefore, Scheller *et al.* does not teach or suggest this limitation.

Scheller *et al.* teaches chimeric proteins containing either androgen or glucocorticoid DNA binding domains. Androgen and glucocorticoid DNA binding domains contain C4 zinc-finger peptides, not C2H2 zinc-finger peptides. Thus,

Scheller *et al.* does not teach or suggest a zinc-finger peptide containing modular units from a C2H2 zinc-finger peptide as required by claim 32.

Thus Scheller *et al.* fails to teach or suggest elements of claim 1 and claim 32 including the use of at least 3 zinc fingers. With respect to claim 1 and dependent claims, Scheller fails to teach or suggest modification of the LBD to alter its specificity for exogenous and endogenous ligands compared to the receptor from which the LBD is obtained. With respect to claim 32 Scheller *et al.* fails to teach or suggest a viral vector nor nucleic acid encoding a fusion protein that includes a DBD that contains zinc fingers with a C2H2 motif.

Sibson *et al.*

Sibson *et al.* fails to cure these deficiencies. Sibson *et al.* is directed to nucleic acid fragments isolated from brain adrenal tissue, placenta or bone marrow and use of such fragments. Sibson *et al.* teaches the incorporation of such nucleic acid fragments into an E. coli plasmid vector and transformation of E. coli cells for expression of corresponding proteins. Sibson *et al.* also teaches that corresponding monoclonal or polyclonal antibodies to these proteins can be prepared. Sibson *et al.* does not teach or suggest any transcriptional regulatory proteins. Specifically, Sibson *et al.* does not teach or suggest preparation of a any ligand activated transcriptional regulators, nor does it teach or suggest the use of at least three zinc fingers in such regulator compared to two in the native DBD in the GR and AR receptors of Scheller *et al.* Further, Sibson *et al.* does not teach or suggest DNA binding domains containing C2H2 zinc-finger peptides (claim 32).

Thus, as described in more detail below, the combination of teachings of the cited references does not result in the instantly claimed methods. None of the references, singly or in any combination thereof, teaches or suggests the claimed fusion proteins, vectors, cells, combinations, and delivery systems.

The combination of teachings of Scheller *et al.* with Sibson *et al.* fails to result in the claimed subject matter

Assuming arguendo that the one of ordinary skill in the art would have been motivated to have combined the AR-GR chimeric receptors taught by Scheller *et al.* with the E.coli plasmid cloning vector taught by Sibson *et al.*, the combination fails to result in the claimed subject matter. Claim 1 and claims dependent thereon, including claim 70 directed to a non-viral delivery system, requires a modification in the ligand binding domain of the fusion protein that changes its ligand specificity compared to the native intracellular receptor from which it originates. As discussed above, the ligand binding domain in the chimeric receptors of Scheller *et al.* retains its native ligand specificity. Furthermore, all claims require that the ligand activated transcriptional regulators (fusion proteins) contain at least **three** zinc finger modules. Claim 32 further requires that the zinc fingers have a C2H2 motif.

Sibson *et al.* does not cure the deficiencies of Scheller *et al.* Sibson *et al.* does not teach or suggest ligand activated transcriptional regulators nor substitution of three zinc finger modules for two zinc finger modules in the AR and GR receptors of Scheller *et al.* nor does Sibson *et al.* suggest substituting the C4 motif of the DBD of the GR and AR receptors with a C2H2 motif (claim 32 and dependents). Further Sibson *et al.* does not teach or suggest modifying a ligand binding domain of a hormone receptor modified to change its ligand specificity compared to the native hormone receptor from which the ligand binding domain originates.

Conclusion

Therefore, the combination of teachings of the references does not result in the instantly claimed subject matter. With respect to all claims, neither reference, singly or in any combination thereof teaches or suggest employing 3 zinc finger modules to bind to and recognize at least 9 contiguous nucleotides rather than 6. With respect to claim 1 and dependent claims, the cited references, singly or in any combination thereof fail to teach or suggest

modification of the LDB to alter specificity for exogenous and endogenous ligands. With respect to claim 32 and dependent claims, the cited references, singly or in any combination fail to suggest selection of a C2H2 motif in place of the C4 motif. Therefore, the Examiner has failed to set forth a case of *prima facie* obviousness.

* * *

In view of the above amendments and remarks, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,
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